

SPECIAL FOCUS ISSUE: CARDIOVASCULAR HEALTH PROMOTION

THE PRESENT AND FUTURE: COUNCIL PERSPECTIVES

Trending Cardiovascular Nutrition Controversies



Andrew M. Freeman, MD,^a Pamela B. Morris, MD,^b Neal Barnard, MD,^c Caldwell B. Esselstyn, MD,^d Emilio Ros, MD, PhD,^e Arthur Agatston, MD,^f Stephen Devries, MD,^{g,h} James O'Keefe, MD,ⁱ Michael Miller, MD,^j Dean Ornish, MD,^k Kim Williams, MD,^l Penny Kris-Etherton, PhD^m

ABSTRACT

The potential cardiovascular benefits of several trending foods and dietary patterns are still incompletely understood, and nutritional science continues to evolve. However, in the meantime, a number of controversial dietary patterns, foods, and nutrients have received significant media exposure and are mired by hype. This review addresses some of the more popular foods and dietary patterns that are promoted for cardiovascular health to provide clinicians with accurate information for patient discussions in the clinical setting. (J Am Coll Cardiol 2017;69:1172-87)

© 2017 by the American College of Cardiology Foundation.

NUTRITION AND CARDIOVASCULAR DISEASE

A heart-healthy diet has been the cornerstone of atherosclerotic cardiovascular disease (ASCVD) prevention and treatment for decades. Contemporary guidance by the American Heart Association/American College of Cardiology (AHA/ACC), the U.S. Department of Agriculture, and the Department of Health and Human Services is issued now as food-

based dietary patterns with accompanying specific nutrient recommendations (e.g., saturated fat, sodium) (1-5). The potential cardiovascular (CV) benefits of specific individual components of the "food-ome" (defined as the vast array of foods and their constituents) are still incompletely understood, and nutritional science continues to evolve. There are important challenges to establishing the scientific evidence base in nutrition, in part because of the

The views expressed in this paper by the ACC's Prevention of Cardiovascular Disease Council do not necessarily reflect the views of the Journal of the American College of Cardiology or the American College of Cardiology.

From the ^aDivision of Cardiology, Department of Medicine, National Jewish Health, Denver, Colorado; ^bMedical University of South Carolina, Charleston, South Carolina; ^cGeorge Washington University School of Medicine; Physicians Committee for Responsible Medicine, Washington, DC; ^dCleveland Clinic Wellness Institute, Cleveland, Ohio; ^eLipid Clinic, Endocrinology and Nutrition Service, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Hospital Clínic, Barcelona and Ciber Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, Madrid, Spain; ^fHerbert Wertheim College of Medicine, Florida International University and Baptist Health of South Florida, Miami, Florida; ^gGaples Institute for Integrative Cardiology, Deerfield, Illinois; ^hNorthwestern University Feinberg School of Medicine, Chicago, Illinois; ⁱSaint Luke's Mid America Heart Institute, Kansas City, Missouri; ^jUniversity of Maryland School of Medicine, Baltimore, Maryland; ^kPreventive Medicine Research Institute, Sausalito, California and University of California-San Francisco, San Francisco, California; ^lRush University Medical Center, Chicago, Illinois; and the ^mDepartment of Nutritional Sciences, Pennsylvania State University, University Park, Pennsylvania. Dr. Freeman has done nonpromotional speaking with Boehringer Ingelheim. Dr. Morris has served on advisory boards for Amgen, AstraZeneca, and Sanofi Regeneron. Dr. Ros has received grants for research through his institution from the California Walnut Commission and is a nonpaid member of its Scientific Advisory Committee. Dr. Miller is a Scientific Advisor for Pressed Juicery. Dr. Ornish consults with Healthways and TerraVia, and receives royalties as an author and honoraria as a speaker. Dr. O'Keefe has a financial interest in Cardiotabs, a nutritional supplement company; and has done promotional speaking for Boehringer Ingelheim, Amgen, and Sanofi Regeneron. Dr. Kris-Etherton serves on the California Walnut Commission Scientific Advisory Committee, Avocado Nutrition Sciences Advisors, Seafood Nutrition Partnership Scientific and Nutrition Advisory Council, McDonald's Global Advisory Council, and the TerraVia Scientific Advisory Board, and has research funding from the California Walnut Commission, Canola Oil Council, McCormick Spice Institute, and National Cattlemen's Beef Association.

Manuscript received August 19, 2016; revised manuscript received October 24, 2016, accepted October 26, 2016.



Listen to this manuscript's audio summary by JACC Editor-in-Chief Dr. Valentin Fuster.



complex interplay between nutrients and confounding by other healthy lifestyle behaviors associated with changes in dietary habits. However, in the meantime, several controversial dietary patterns, foods, and nutrients have received significant media exposure and are mired by hype. This review addresses some of the more popular food trends and dietary patterns that are promoted for CV health to provide clinicians with accurate information for patient discussions in the clinical setting.

CHALLENGES IN NUTRITION SCIENCE

Decades of research have significantly advanced our understanding of the role of diet in the prevention and treatment of ASCVD. The totality of evidence includes randomized controlled trials (RCTs), cohort studies, case-control studies, and case series/reports as well as systematic reviews and meta-analyses (6). Although a robust body of evidence from RCTs testing nutritional hypotheses is available, it is not feasible to obtain meaningful RCT data for all diet and health relationships. Studying preventive diet effects on ASCVD outcomes requires many years because atherosclerosis develops over decades and may be cost-prohibitive for RCTs (7). Most RCTs are of relatively short duration and have limited sample sizes. Dietary RCTs are also limited by frequent lack of blinding to the intervention and confounding resulting from imperfect diet control (replacing 1 nutrient or food with another affects other aspects of the diet). In addition, some diet and health relationships cannot be ethically evaluated (8). For example, it would be unethical to study the effects of certain nutrients (e.g., sodium, trans fat) on cardiovascular disease (CVD) morbidity and mortality because they increase major risk factors for CVD.

Epidemiological studies have suggested associations among diet, ASCVD risk factors, and ASCVD events. Prospective cohort studies yield the strongest observational evidence because the measurement of dietary exposure precedes the development of the disease (6). However, limitations of prospective observational studies include: imprecise exposure quantification; collinearity among dietary exposures (e.g., dietary fiber tracks with magnesium and B vitamins); consumer bias, whereby consumption of a food or food category may be associated with non-dietary practices that are difficult to control (e.g., stress, sleep quality); residual confounding (some nondietary risk factors are not measured); and effect modification (the dietary exposure varies according to individual/genetic characteristics). It is important

to highlight that many healthy nutrition behaviors occur with other healthy lifestyle behaviors (regular physical activity, adequate sleep, no smoking, among others), which may further confound results.

Case-control studies are inexpensive, relatively easy to do, and can provide important insight about an association between an exposure and an outcome. However, the major limitation is how the study population is selected or how retrospective data are collected (9). In nutrition studies that involve keeping a food diary or collecting food frequency information (i.e., recall or record), accurate memory and recording of food and nutrient intake over prolonged periods can be problematic and subject to error, especially before the diagnosis of disease. The advent of mobile technology and food diaries may provide opportunities to improve accuracy of recording dietary intake and may lead to more robust evidence.

Finally, nutrition science has been further complicated by the influences of funding from the private sector, which may have an influence on nutrition policies and practices (10).

HEALTHY DIETARY PATTERNS AND ASCVD RISK

Each year patients are bombarded with the publication of new “miracle” diet books that claim to promote health, effect weight loss, and reduce disease risks. Although the scientific evidence base for some of these diets is limited, there are several dietary patterns that have clearly been demonstrated to reduce the risk of many chronic diseases, including coronary heart disease (CHD). Clinicians must have an understanding of the specific common attributes of these healthy dietary patterns as a foundation for evaluating the health claims of new, widely hyped diets. Evidence-based healthy dietary patterns are high in fruits, vegetables, whole grains, legumes, and nuts in moderation, although some may include limited quantities of lean meats (including poultry and seafood), low-fat dairy products, and liquid vegetable oils (Table 1). These dietary patterns are also low in saturated, trans, and solid fats; sodium; added sugars; and refined grains.

The 2015 to 2020 Dietary Guidelines for Americans recommend 3 healthy eating patterns: 1) the Healthy U.S.-style Eating Pattern; 2) the Healthy

ABBREVIATIONS AND ACRONYMS

- ASCVD** = atherosclerotic cardiovascular disease
- BMI** = body mass index
- CD** = celiac disease
- CHD** = coronary heart disease
- CI** = confidence interval
- CV** = cardiovascular
- CVD** = cardiovascular disease
- GRD** = gluten-related disorder
- HDL-C** = high-density lipoprotein cholesterol
- HR** = hazard ratio
- LDL-C** = low-density lipoprotein cholesterol
- MI** = myocardial infarction
- MUFA** = monounsaturated fatty acids
- NCGS** = nonceliac gluten sensitivity
- NO** = nitric oxide
- PUFA** = polyunsaturated fatty acids
- RCT** = randomized controlled trial
- RR** = relative risk
- SFA** = saturated fatty acids
- T2DM** = type 2 diabetes mellitus
- VCO** = virgin coconut oil

TABLE 1 Clinical Recommendations for Specific Dietary Patterns, Foods, and Nutrients

Nutrition/Food Item	Level of Evidence Available and Included in This Paper	Recommendations for Patients
Dietary pattern with added fats, fried food, eggs, organ and processed meats, and sugar-sweetened beverages (<i>Southern</i> diet pattern)	Prospective studies	Avoid
Dietary cholesterol	RCTs and prospective studies along with meta-analyses	Limit
Canola oil	RCT meta-analyses show improvement in lipids but no prospective studies or RCTs for CVD outcomes	In moderation
Coconut oil	RCT meta-analyses and observational studies on adverse lipid effects. No prospective studies or RCTs for CVD outcomes	Avoid
Sunflower oil	No prospective studies or RCTs for CVD outcomes	In moderation
Olive oil	RCTs supporting improved CVD outcomes	In moderation
Palm oil	RCTs and observation studies showing worsened CVD outcomes	Avoid
Antioxidant-rich fruits and vegetables	RCTs and observational studies showing improved CVD outcomes and improvements in blood lipids	Frequent
Antioxidant supplements	RCTs and prospective and observational studies show potential harm	Avoid
Nuts	RCT and large prospective and meta-analysis studies showing improved CVD outcomes	In moderation
Green leafy vegetables	Large meta-analyses and variably sized observational studies as well as a large prospective study	Frequent
Protein from plant sources	Large observational and prospective studies	Frequent
Gluten-containing foods	Observational studies and RCTs	Avoid if sensitive or allergic

CVD = cardiovascular disease; RCT = randomized controlled trial.

Mediterranean-style Eating Pattern; and 3) the Healthy Vegetarian Eating Pattern (11). Health care practitioners should become familiar with these food-based dietary patterns to effectively educate patients on heart-healthy nutrition recommendations.

Evidence for the benefits of a healthy dietary pattern was reported in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study (12). This national, population-based, longitudinal study of white and black adults >45 years of age (enrolled from 2003 to 2007) evaluated 5 dietary patterns in 17,418 participants: *convenience*, *plant-based*, *sweets*, *Southern*, and *alcohol and salad*. The *Southern* pattern, which was high in added fats, fried food, eggs, organ and processed meats, and sugar-sweetened beverages, was the most deleterious. The *Southern* pattern was associated with a 56% increase in acute CHD events over <6 years of follow-up. There was also a 50% increase in mortality in patients with chronic kidney disease and a 30% increase in stroke with this diet. Greater consumption of the *Southern* pattern was associated with a higher likelihood of smoking, a lower likelihood of being physically active, and higher mean body mass index (BMI) and waist circumference compared with lower consumption. Finally, greater consumption of the *Southern* pattern was associated with a higher prevalence of hypertension, dyslipidemia, and type 2 diabetes mellitus (T2DM).

Recent findings from a large cohort from the NHS (Nurses' Health Study) and HPFS (Health Professionals Follow-up Study) also suggests a significant increased risk of mortality with higher trans and saturated fat intakes, but lower mortality with unsaturated fat, both polyunsaturated and monounsaturated fats. In addition, all sources of animal protein (eggs, fish, poultry, red meat, and processed red meat) were noted to increase all-cause mortality relative to vegetable protein, with processed red meat being associated with more CV deaths and egg consumption being associated with more cancer deaths (13).

There is evidence that a healthy diet pattern is beneficial for patients with clinical ASCVD. The ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial) and TRANSCEND (Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease) studies evaluated older women and men (mean age 66.5 years, n = 31,546) with CVD or T2DM who were also receiving drugs for secondary prevention (14). Two dietary indexes (not part of the RCT) were used for assessment: the modified Alternative Healthy Eating Index and the Diet Risk Score. The primary outcome was a composite of CV death, myocardial infarction (MI), stroke, or congestive heart failure. Patients in the healthier quintiles of modified Alternative Healthy Eating Index scores had a significantly lower risk of ASCVD (hazard ratio [HR]:

0.78; 95% confidence interval [CI]: 0.71 to 0.87, top vs. lowest quintile of modified Alternative Healthy Eating Index). The reductions in risk for CV death, MI, and stroke were 35%, 14%, and 19%, respectively. The protective association was consistent regardless of whether patients were receiving pharmacotherapy.

In the NHS and HPFS, which included 4,098 participants who survived an initial coronary event, the association of post-MI diet quality with all-cause and CVD mortality was evaluated (15). Diet was assessed using a validated food frequency questionnaire every 4 years. After nearly 9 years of follow-up, among those participants with the greatest improvement in diet quality from pre- to post-MI, there was a 29% reduction in all-cause mortality and a 40% reduction in CVD mortality comparing extreme quintiles of the Healthy Eating Index.

A recent report of the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial of 15,482 patients with stable CHD from 39 countries demonstrated that greater adherence to a Mediterranean-style dietary pattern reduced major CVD events. After 3.7 years of follow-up, there was a 5% reduction in CVD for each 1-point increase in a Mediterranean diet score when the score was >12 (Mediterranean diet score categories were ≤12, 13-14, and ≥15, representing increasing number of food groups included in the traditional Mediterranean diet) (16).

HEALTHY DIETARY PATTERNS: THE BOTTOM LINE. Current evidence strongly supports the Healthy U.S. Dietary Pattern, the Healthy Mediterranean-Style Dietary Pattern, and the Healthy Vegetarian Dietary Pattern for ASCVD risk reduction and improvement in ASCVD risk factors for adults and children 2 years of age and older (1-5). Healthy dietary patterns emphasize high intake of fruits, vegetables, whole grains, legumes, and nuts in moderation, and may include limited quantities of lean meat, fish, low-fat and nonfat dairy products, and liquid vegetable oils (Table 2). These dietary patterns are also low in saturated, trans, and solid fats; sodium; added sugars; and refined grains. In addition, energy intake and physical activity appropriate for maintaining a normal weight, and achieving nutrient adequacy are also recommended.

NUTRITION HYPES AND CONTROVERSIES

EGGS AND DIETARY CHOLESTEROL: WHAT'S THE TRUTH? Dietary cholesterol increases blood cholesterol concentrations (17,18). Nonetheless, the 2015 Dietary Guidelines Advisory Committee reported that “available evidence shows no appreciable

relationship between consumption of dietary cholesterol and serum cholesterol” (19). This statement was widely reported in the press and resulted in significant consumer confusion. Although the 2015-2020 Dietary Guidelines for Americans concluded that “individuals should eat as little dietary cholesterol as possible,” this statement attracted little media attention. Many patients have embraced only the committee’s initial “no risk” conclusion and missed the final conclusion that limitation of dietary cholesterol is indeed an important issue.

Although saturated and trans fats have the greatest effect on blood cholesterol concentrations, blood cholesterol concentrations also rise in response to cholesterol in foods. Within the range of cholesterol intakes in typical omnivorous diets, the relationship is linear. At higher cholesterol intakes, the relationship is curvilinear; changes in dietary cholesterol have less of an effect on serum cholesterol (20). In a meta-analysis of 17 studies with 556 subjects that evaluated different amounts of dietary cholesterol from eggs, the addition of 100 mg/day of dietary cholesterol was predicted to increase total cholesterol by 2.17 mg/dl, low-density lipoprotein-cholesterol (LDL-C) by 1.93 mg/dl, and high-density lipoprotein-cholesterol (HDL-C) by 0.31 mg/dl (21). The magnitude of the effect differs from 1 person to another, largely from differences in the baseline diet as well as genetically determined intestinal cholesterol absorptive capacity (i.e., hyporesponders vs. hyperresponders) (22). As baseline cholesterol intake increases, the effect of further increases in dietary cholesterol is less noticeable. A recent meta-analysis of RCTs further supports the serum cholesterol-raising effect of dietary cholesterol (obtained mainly from eggs) (23).

Eggs and dietary cholesterol: the bottom line. Despite the widespread enthusiasm with the original statement of the 2015 Dietary Guidelines Advisory Committee Report, it remains prudent to advise patients to significantly limit intake of dietary cholesterol in the form of eggs or any high-cholesterol foods to as little as possible. Whereas shellfish is also a source of dietary cholesterol, it is low in saturated fatty acids (SFAs) (24) and may be a better choice than foods high in SFA, but should be limited to reduce dietary intake of cholesterol.

VEGETABLE OILS: WHICH TO USE AND WHY? Vegetable oils vary greatly in the content of SFAs, monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs). The tropical oils, coconut oil and palm oil, are high in SFAs. In contrast, canola, olive, and sunflower oils are high in MUFAs.

TABLE 2 Summary of Key Evidence to Support Recommendations

Nutrition/Food Item	Key Publication(s) on the Topic, Year (Ref. #)	Brief Summary of the Study	Key Conclusion
Dietary pattern with added fats, fried food, eggs, organ and processed meats, and sugar-sweetened beverages (<i>Southern</i> dietary pattern)	Shikany et al., 2015 (12)	1. In 17,418 subjects without CVD, nutrition surveys were classified into 5 eating patterns: convenience; plant-based (although containing dairy, poultry, and fish); sweets-based; alcohol/salad; and the Southern pattern, characterized by fried foods and added fats, eggs and egg dishes, organ meats, processed meats, and sugar-sweetened drinks. There was a 56% increase in cardiac events over 6 yrs with the Southern pattern, which was eaten more frequently by residents of the Stroke Belt who were male, black, smokers, less educated, impoverished, physically inactive, and overweight/obese.	1. A dietary pattern characteristic of the Southern United States (animal products and sweets) was associated with greater hazard of CHD, and is more common in overweight, Southern black men with lower levels of education and economic status.
Dietary cholesterol	Hopkins, 1992 (20) Weggemans et al. 2001 (21)	1. Meta-analysis including 27 studies using prepared diets and assessing effects on cholesterol. 2. Meta-analysis of 17 studies on the effect of cholesterol from eggs.	1. Added dietary cholesterol increases serum cholesterol; the effect is greatest when baseline intake is low. 2. Each 100-mg increment in dietary cholesterol increases TC by 2.2 mg/dl and increases the TC:HDL ratio by 0.02 units.
Canola oil	Lin et al. 2013 (36)	1. Systematic review of 31 RCTs concluded that canola oil reduces LDL-C but has no effect on HDL-C, lipid peroxidation, or inflammation. There are no data on CVD outcomes.	As a plant-based oil rich in unsaturated fatty acids, canola oil can be used to replace other fats, but by being refined is devoid of polyphenols.
Coconut oil	Eyres et al. 2016 (32)	1. Review of observational studies and RCTs reported a cholesterol-raising association/effect of coconut oil. There are no data on CVD outcomes.	Because coconut oil is rich in SFA, its use is not recommended.
Sunflower oil	Bester et al., 2010 (46)	1. Review of the CV effects of various oils concluded that sunflower oil reduces LDL-C with no clear effect on HDL-C when replaced with other fats/oils. No effects on CVD outcomes have been reported.	Sunflower oil is rich in MUFAs and PUFAs, and as such can be used to replace other fats.
Olive oil	Schwingshackl et al. 2015 (42) Schwingshackl, et al., 2014 (43) Estruch et al., 2013 (45)	1. Meta-analysis of RCTs demonstrated beneficial effects of olive oil on inflammation and oxidative status. 2. Large meta-analysis of cohort studies concluded that olive oil was associated with reduced risk of all-cause mortality, CVD, and stroke. 3. In the PREDIMED nutrition intervention RCT, a Mediterranean diet supplemented with extra-virgin olive oil at 50 mL/d for 5 yrs reduced incident CVD by 30% compared with a lower-fat control diet.	Extra-virgin (unrefined) olive oil is rich in MUFA and polyphenols and there is consistent evidence of its beneficial effect on CVD risk markers and CVD morbidity and mortality. There is sufficient evidence to recommend its use.
Palm oil	Sun et al., 2015 (33) Kabagambe et al., 2005 (35)	1. Meta-analysis of RCTs comparing palm oil to other vegetable oils demonstrates a cholesterol-raising effect. 2. Case-control study reported an association between palm oil consumption and CHD.	Of all vegetable oils, palm oil is among the highest in SFAs and, consequently, increases risk of CHD. Consumption should be discouraged.
Antioxidant-rich fruits and vegetables	Cassidy et al., 2013 (51) Johnson et al., 2015 (52)	1. Prospective cohort study of 93,600 women in the NHS II evaluated the relationship between anthocyanin intake and the risk of myocardial infarction during an 18-yr follow-up. 2. An 8-week, randomized, double-blind, placebo-controlled trial evaluated the effect of daily blueberry consumption on blood pressure.	1. A 32% reduced risk of myocardial infarction was observed in those with the highest vs. lowest quintile of anthocyanin intake (especially blueberries and strawberries). 2. The equivalent of 1 cup of blueberries/day resulted in blood pressure reduction of 7 mm Hg systolic and 5 mm Hg diastolic.
Antioxidant supplements	Gruppo et al. 1999 (71) Vivekananthan et al. 2003 (72)	1. RCT of 11,324 post-infarct patients given omega-3 fatty acids (1 g daily, n = 2,836), vitamin E (300 mg daily, n = 2,830), both (n = 2,830), or none (control, n = 2,828) for 3.5 yrs with a combined endpoint of death, nonfatal myocardial infarction, and stroke. 2. Meta-analysis of RCTs of β -carotene trials including a total of 138,113 patients with CHD and mortality outcomes.	Neither vitamin E nor β -carotene supplements prevent CHD or all-cause mortality.
Nuts	Sabaté et al. 2010 (87) Luo et al. 2014 (91) Estruch et al. 2013 (45)	1. Pooled analysis of data from 25 RCTs reported a dose-related cholesterol-lowering effect of nut-enriched diets compared with different control diets. 2. Large meta-analysis indicated that nut consumption is inversely associated with CHD, overall CVD, and all-cause mortality, but not significantly associated with diabetes and stroke. 3. The PREDIMED nutrition intervention RCT demonstrated that a high vegetable fat Mediterranean diet supplemented with mixed nuts at 30 g/d for 5 yrs reduced incident CVD by 30% compared with a lower-fat control diet.	Nuts are a nutrient-dense, heart-healthy food with a favorable fatty acid profile.

Continued on the next page

TABLE 2 Continued

Nutrition/Food Item	Key Publication(s) on the Topic, Year (Ref. #)	Brief Summary of the Study	Key Conclusion
Green leafy vegetables	Li et al. 2014 (105) Joshi et al. 2009 (110)	<ol style="list-style-type: none"> 1. A large meta-analysis of 434,342 participants found that for each increment of 0.2 servings daily (approximately 1 oz), there was a 13% lower risk of developing T2DM. 2. In the NHS and the HPFS, in which nearly 110,000 women and men were followed for 14–16 yrs, 3 servings/day of green leafy vegetables, combined with a low-carbohydrate diet, elicited a 24% reduced risk of CVD. 	Green leafy vegetables (3 servings daily) reduce the risk of incident T2DM and CVD.
Protein from plant sources	Connor et al. 1978 (126) Campbell et al. 1998 (124) Song et al. 2016 (136)	<ol style="list-style-type: none"> 1. Over a 4-yr period, 528 healthy Tarahumara Indians were surveyed for plasma lipids and lipoproteins. Diet consisted of 12% fat, 13% protein, 75% carbohydrate. The average total cholesterol in adults was 136 mg/dl. The average blood pressure for adults was 111/73 mm Hg. Corn and beans provided 90% of total calories. In the Tarahumara diet, 96% of protein is from corn and beans. 2. Blood, urine, food samples, and dietary data were collected from 6,500 persons from rural China. Mean serum cholesterol was 127 mg/dl. Animal protein intake was only 10% of the U.S. intake. Mean BMI was 20.5. The dietary fat was 14%, carbohydrate 71%, and protein 10% of calories. 3. Participants from the Nurses' Health Study were studied from 1980 to 2012 and the Health Professionals Follow-up Study were studied from 1986 to 2012 (n = 131,342). Plant protein intake was assessed by validated food frequency questionnaires. 	<ol style="list-style-type: none"> 1. In this population thriving on plant protein (corn and beans), investigators did not identify a single overweight man nor any Tarahumara with hypertension during the 4-yr study of this Indian population consuming an antiatherogenic plant-based dietary pattern. 2. Coronary mortality rates in China observed for ages 0–64 yrs in this group were 4.0 per 100,000 for men and 3.4 for women compared with 66.8 per 100,000 men and 18.9 per 100,000 women in the United States. 3. Plant protein intake was associated with lower cardiovascular mortality (HR: 0.88 per 3% energy increment; 95% CI, 0.80 to 0.97; P for trend = 0.007).
Gluten-containing foods	Dickey et al. 2006 (140). Ebbeling et al. 2012 (145).	<ol style="list-style-type: none"> 1. Retrospective review of 371 patients with CD and evaluation of outcomes including weight loss. 2. A small, controlled 3-way crossover study of 21 overweight or obese young adults and its effects on weight loss. 	<ol style="list-style-type: none"> 1. A gluten-free diet is not necessarily associated with weight loss. 2. A gluten-free, low glycemic index diet can increase resting energy expenditure and promote weight loss.

BMI = body mass index; CD = celiac disease; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HPFS = Health Professionals Follow-up Study; LDL-C = low-density lipoprotein cholesterol; MUFA = monounsaturated fatty acids; NHS = Nurses' Health Study; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids; T2DM = type 2 diabetes mellitus; TC = total cholesterol; other abbreviations as in Table 1.

Soybean oil, sunflower oil, and corn oil are high in n-6 polyunsaturated fatty acids (PUFAs). Canola oil contains as much as 10% n-3 PUFAs (α -linolenic acid), and soybean oil has about 7%.

Coconut oil is very rich in the SFAs lauric acid (C12:0) and myristic acid (C14:0). Lauric acid is a medium-chain fatty acid and is rapidly absorbed, taken up by the liver, and oxidized for energy production (25). Both lauric and myristic acids have a similar total cholesterol- and LDL-C-raising effect, but also raise HDL-C more than other fatty acids (26,27). Virgin coconut oil (VCO) retains the bioactive polyphenols lost in refinement and has been promoted for supposed CV benefits (28). However, there is little evidence for ASCVD risk reduction with the incorporation of virgin coconut oil and available evidence is of low methodological rigor. Irrespective of this, VCO is very high in SFAs and should be avoided. Evidence with regard to VCO and its CV benefits is at a very early stage and limited to animal studies and a few human trials (29). No prospective studies have evaluated coconut oil exposure in relation to CVD outcomes, but ecological data indicate that Asian populations who have coconut as their staple food

have a low incidence of ASCVD (30); however, these populations do not consume much saturated fat from other food sources. The National Lipid Association concluded that there is no evidence of any health benefit of coconut oil, and if consumed, it must be done within the context of recommendations for SFA intake for the management of dyslipidemia (31). A recent review of 21 research papers including 8 clinical trials and 13 observational studies reported that coconut oil generally raised total and LDL-C, but to a lesser extent than butter (32). The evidence from the intervention studies demonstrated that replacing coconut oil with unsaturated fats decreased total and LDL-C, which would be expected to decrease CVD risk.

Compared with most other vegetable oils, except coconut oil, palm oil is high in SFAs, mostly palmitic acid. A recent meta-analysis of 32 RCTs concluded that, compared with vegetable oils low in SFAs, palm oil resulted in mean increases of 0.24 mmol/l (9.3 mg/dl) LDL-C and 0.02 mmol/l (0.8 mg/dl) HDL-C, which demonstrated a proportionately greater increase in LDL-C than HDL-C (33). Thus, palm oil may be associated with increased ASCVD risk. Ecological data

suggest that rapidly increasing ASCVD rates in developing countries may relate, in part, to increased SFA intake from palm oil use (34). In addition, a case-control study in Costa Rica observed a positive association between palm oil consumption and CHD (35). Participants who typically used palm oil for cooking had 33% and 23% higher CHD risk than those using soybean oil or sunflower oil, respectively. No RCTs using palm oil for CVD outcomes have been performed.

Canola oil is low in SFAs and high in MUFAs and PUFAs, including linoleic and α -linolenic acids. A recent systematic review of 31 RCTs concluded that canola oil reduced LDL-C, but had no effect on HDL-C, lipid peroxidation, or inflammation (36). No prospective studies or RCTs have examined the effects of canola oil on CVD outcomes.

A recent study compared the effects of PUFA-rich corn oil with extra-virgin olive oil on plasma lipids and lipoproteins in men and women with elevated LDL-C (≥ 130 mg/dl and < 200 mg/dl) (37). After 21 days of consuming 4 tablespoons of either corn oil or extra-virgin olive oil, LDL-C decreased 10.9% versus 3.5%, respectively. This was attributed to the higher PUFA content of corn oil.

MUFA-rich olive oil is the principal source of fat in the Mediterranean diet, as consumed in Mediterranean countries. When substituted for SFAs or carbohydrates, MUFAs have been demonstrated to reduce LDL-C and increase HDL-C, thus decreasing the total cholesterol: HDL-C ratio (38). Unlike other edible oils, the cardioprotective and other healthy properties of olive oil have been assessed in many cohort studies and RCTs that have examined both CVD biomarkers and ASCVD outcomes.

Feeding trials testing virgin olive oil-rich diets compared with other healthy diets have confirmed the LDL-C-lowering and HDL-C-raising effect (39,40). The beneficial effect of virgin olive oil may be due in part to polyphenol content and associated antioxidant activity, which may improve HDL functionality (41). In an RCT with 47 healthy volunteers, use of polyphenol-rich olive oil significantly improved HDL-C efflux capacity when compared with use of a polyphenol-poor olive oil. These polyphenols increased HDL size, promoted greater HDL stability, reflected as a triglyceride-poor core, and enhanced HDL oxidative status through an increase in the olive oil polyphenol metabolites content in the lipoprotein. RCTs have also demonstrated beneficial effects of olive oil on markers of endothelial function and inflammation (42). A recent meta-analysis of 32 cohort studies relating exposure to MUFAs (of both plant and animal origin), olive oil, oleic acid, and the

MUFA: SFA ratio to various health outcomes indicated that, when comparing the upper to the lower tertile of consumption, olive oil was associated with reduced risk of all-cause mortality, CVD events, and stroke (43). A recent report from the prospective cohort of the Nurses' Health Study, a U.S. population with low average olive oil consumption, supports a modest inverse relationship between olive oil exposure and risk of T2DM (44).

Because virgin olive oil was used in 1 of the arms of the PREDIMED (Prevención con Dieta Mediterránea) RCT, testing Mediterranean diets for primary CV prevention, there is first-level scientific evidence of the health benefits of extra-virgin olive oil (45). After approximately 5 years, PREDIMED participants assigned to the Mediterranean diet plus virgin olive oil arm experienced a mean 30% reduction in the primary endpoint, which was a composite of MI, stroke, and CVD death. For secondary endpoints, stroke events were decreased by 34%; however, there was no decrease in death from CV causes compared with controls.

No RCTs have compared diets including olive oil with low-fat vegetarian or vegan diets, or to Asian diets that typically do not use olive oil, for any health outcomes. Olive oil is similar in energy density to other fats, and although its SFA content (approximately 14%) is lower than that of animal fats (approximately 30% for chicken), it is higher than for most legumes, vegetables, fruits, or grains.

Sunflower oil is rich in both MUFAs and n-6 PUFAs, low in SFAs, and almost devoid of n-3 PUFAs. RCTs have demonstrated the cholesterol-lowering effect of sunflower oil, but the effect on HDL-C remains unclear (46). No other cardioprotective effects have been observed. No epidemiological or RCT data on sunflower oil and CVD events are available.

Vegetable oils: the bottom line. Solid fats (at room temperature), including coconut oil and palm oil, have deleterious effects on ASCVD risk factors. Current claims of documented health benefits of the tropical oils are unsubstantiated and use of these oils should be discouraged.

In contrast, liquid vegetable oils have beneficial effects on lipids and lipoproteins. As noted, they decrease LDL-C and, compared with dietary carbohydrates, they increase HDL-C and decrease triglycerides (47). The evidence base for olive oil is the most comprehensive, with clear evidence for a benefit in ASCVD risk reduction. The 2015 to 2020 Dietary Guidelines for Americans support the use of liquid vegetable oils within the context of a calorie-controlled, heart-healthy diet to decrease ASCVD risk (11).

BERRIES AND BRIGHTLY COLORED VEGETABLES: THE ROLE OF ANTIOXIDANTS. The United States has been in the midst of a “berry boom,” and in 2014, berries were the third most frequently consumed fruits, behind only bananas and apples (48). Although improved production and year-round availability have played a role, certainly the “super-food” factor has also been important. Anthocyanins are a subclass of antioxidant phytochemicals known as flavonoids, and are strongly concentrated in blueberries, strawberries, raspberries, red cabbage, red radishes, and eggplant (purple vegetables) (49). Anthocyanins have potent anti-inflammatory properties and scavenge free radicals. They regulate endothelial nitric oxide (NO) production, modulate endothelial function, and influence glucose metabolism with salutary effects on insulin resistance and B-cell dysfunction (50).

In the Nurses’ Health Study II, participants with the highest versus the lowest quintile of anthocyanin intake had an HR for MI of 0.68 (95% CI: 0.49 to 0.96; $p = 0.03$) (51). Combined intake of >3 servings/week of blueberries and strawberries, the 2 most common food sources of anthocyanins, had a trend toward decreased risk of MI (HR: 0.66; 95% CI: 0.40 to 1.08).

Anthocyanin-associated changes in blood pressure and NO levels were evaluated in an 8-week, randomized, double-blinded, placebo-controlled trial of post-menopausal women (52). Women consumed the equivalent of 1 cup of fresh blueberries, 22 g of freeze-dried blueberry powder, or, as a control, 22 g of control powder. Systolic blood pressure decreased from 138 ± 14 mm Hg to 131 ± 17 mm Hg ($p < 0.05$) and diastolic pressure from 80 ± 7 mm Hg to 75 ± 9 mm Hg ($p < 0.01$).

The association between anthocyanins and the risk of diabetes was evaluated in the Nurses’ Health Study I and II and the Health Professionals Follow-Up Study (53). Intake of ≥ 2 servings/week of anthocyanin-rich foods, especially blueberries, was associated with a pooled HR of 0.77 for the risk of T2DM compared with <1 serving/month (95% CI: 0.68 to 0.87; $p_{\text{trend}} < 0.001$). No association was identified between other flavonoid subclasses and the risk of diabetes. Among more than 10 fruits studied, blueberry intake was associated with the lowest risk of diabetes with a pooled HR of 0.74 with intake of 3 servings/week (95% CI: 0.66 to 0.83).

Antioxidants: to supplement or not to supplement? In view of the evidence that fruits and vegetables protect against heart disease, many forms of cancer, and other chronic diseases, and may also help slow the aging process, the media and the

supplement industry began to promote the benefits of antioxidant supplements long before the results of placebo-controlled RCTs were available (54-56). Research has identified some of the bioactive components that contribute to the beneficial effects of foods rich in antioxidants, including β -carotene, vitamin C, vitamin E, and selenium (57). Many of these compounds scavenge reactive oxygen species, including free radicals, which increase oxidative stress and have been associated with aging, CHD, diabetes, cancer, arthritis, and other chronic diseases as well as Alzheimer’s and Parkinson’s disease (58-65).

Initial observational studies in large populations showed that high-dose antioxidant micronutrient supplement use was associated with decreased heart disease, cancer, and aging (66-68), and this resulted in an increase in supplement intake among U.S. adults (69,70). However, multiple subsequent RCTs of antioxidant supplements reported either neutral or negative results, including the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico)-Prevenzione trial of vitamin E, the Physicians Health Study of β -carotene, and the NIH (National Institutes of Health)-AARP Diet and Health Study of multivitamin supplementation (71-75). In the GISSI-Prevenzione trial, 11,324 patients who had experienced an MI were randomized to a 300-mg vitamin E (α -tocopherol) supplement with or without an omega-3 fatty acid supplement. In an intention-to-treat analysis, omega-3 fatty acid supplementation showed CV benefit (reduction in major adverse CV events), but vitamin E did not (71).

A process known as *hormesis* is hypothesized to explain, in part, the neutral or negative effects of excess antioxidant supplementation. Hormesis is a biphasic dose response to a stressor (toxic chemical, thermal, or radiological) in which a substance is beneficial at low doses but harmful at higher doses. Low doses of oxidant stressors induce endogenous antioxidant production that seems to be protective, but higher doses appear to be ineffective (65,76,77). Thus, although foods rich in antioxidants at physiological levels appear to have health benefits, RCTs of high-dose antioxidant supplements have not demonstrated benefits. Further investigation will be necessary to better define the role of antioxidant supplements in health promotion (78-82).

Berries and antioxidant supplementation: the bottom line. Currently available evidence suggests that fruits and vegetables are the healthiest and most beneficial source of antioxidants for ASCVD risk reduction. There is no evidence of ASCVD benefit

with the addition of high-dose antioxidant dietary supplements.

NUTS FOR CV HEALTH. Nuts include almonds, walnuts, hazelnuts, Brazil nuts, pistachios, pine nuts, and pecans (tree nuts), and also peanuts, which botanically are legumes. The fatty acids in nuts are predominantly unsaturated, with oleic acid being the most abundant. Nuts also contain complex carbohydrate and fiber, protein, tocopherols, nonsodium minerals, phytosterols, and polyphenols (83).

Incorporation of nuts into a healthy dietary pattern has been associated with improvement in ASCVD risk factors. Nut consumption has been inversely correlated with risk of T2DM. In 6 prospective studies, 4 servings of nuts per week were associated with a 13% reduced risk (0.87; 95% CI: 0.81 to 0.94) (84). Furthermore, a pooled analysis of 12 RCTs in patients with T2DM reported that nuts improved glycemic control (85). A meta-analysis of 4 prospective studies relating nut consumption to incident hypertension also demonstrated a protective effect (86). Many short-term RCTs have evaluated the effects of nuts on the lipid/lipoprotein profile. A pooled analysis of 25 RCTs using various nuts demonstrated a consistent cholesterol-lowering effect, with a mean 7.4% LDL-C reduction with consumption of 67 g (2.4 oz) of nuts. The LDL-C-lowering effect was independent of the type of nut tested (87). Participants randomized to the Mediterranean diet with nuts had a lower prevalence of metabolic syndrome in preliminary data from the PREDIMED trial (88), with higher reversion rates noted in the full cohort, owing in part to decreased visceral adiposity (89). The available evidence on the CV benefit of increasing nut consumption has prompted the inclusion of nuts and seeds in many dietary guidelines, including the recent AHA/ACC Guideline on Lifestyle Management to Reduce CVD Risk (90).

Large prospective studies have examined nut consumption and incident CVD, and 3 meta-analyses have recently been published (84,86,91). Six studies reported a consistent protective effect of nut consumption on CVD outcomes, resulting in an inverse association with fatal CVD (relative risk [RR]: 0.76; 95% CI: 0.69 to 0.84) and nonfatal CVD (RR: 0.78; 95% CI: 0.67 to 0.92) per 4 servings of nuts/week (1 serving = 28.4 g). When the results were expressed for each serving/day, the pooled RR for CVD (fatal and nonfatal) was 0.72 (95% CI: 0.64 to 0.81). In all studies, a dose-response relationship between nut consumption and reduced CVD risk was observed. In contrast, the effect of nuts on the risk of stroke has been inconsistent. A meta-analysis of observational

studies found no association between nut consumption and risk of stroke (84). However, in the PREDIMED trial, the Mediterranean diet supplemented with 1 serving (30 g) of mixed nuts/day resulted in a 30% reduction in incident CVD, including a 49% reduction in stroke (45), thus providing first-level evidence of the CV benefit of nuts. The pooled RR for all-cause mortality, ascertained in 5 studies, was 0.83 (95% CI: 0.76 to 0.91) for each serving of nuts/day (86). An additional meta-analysis focusing on mortality concluded that nut consumption is associated with reduced all-cause, CV, and cancer mortality, although residual confounding may have limited interpretation because nut eaters also exhibit healthier lifestyles (92). On the basis of these findings, the AHA/American Stroke Association guidelines currently recommend a Mediterranean dietary pattern that includes nuts and seeds as an effective strategy for the primary prevention of stroke (93).

Nuts are high in fat and are calorically dense. As such, if they are consumed in excess of energy needs, they will cause weight gain. Importantly, however, analyses of large cross-sectional and observational studies show an inverse association between nut consumption and BMI or weight gain over time (94,95). In addition, a recent meta-analysis of RCTs showed a small, nonsignificant association of nut consumption with reduced adiposity (96). Mechanistically, the lack of weight gain after consuming nuts is likely the result of their satiating effect, together with incomplete digestion and a reduction of metabolizable energy (97). Despite the body of evidence reporting benefits of nuts on body weight, a few single studies have reported a small weight gain with nut consumption when participants were instructed to incorporate nuts/peanuts into their diet (98,99).

Nuts and CV health: the bottom line. Nuts may be included for ASCVD risk factor improvement and ASDVD risk reduction as part of a heart-healthy dietary pattern. Portion control is necessary to avoid excess calorie consumption. Clinicians must provide guidance to incorporate nuts isocalorically in the diet by substitution for other foods, preferably those that provide “empty calories.”

GREEN LEAFY VEGETABLES FOR CV HEALTH. The vascular benefits attributable to dark green vegetables include reduced arterial stiffness and blood pressure, resulting in part to enrichment of inorganic nitrate, which undergoes salivary bacterial conversion to nitrite, followed by gastrointestinal acidification to NO. However, the physiological effects begin to wane after 2 days of ingestion, and daily intake of

nitrate-rich foods may be required to maintain the beneficial CV benefits (100). Among green vegetables, nitrate concentrations are most appreciable in arugula, mesclun, and Swiss chard, with smaller amounts in celery, collard greens, green beans, kale, and spinach. In a study of 26 healthy men and women randomized to a chicken sandwich meal with or without a large portion of spinach (8.8 oz containing 220 g nitrate), there were significant reductions in mean systolic blood pressure that peaked 2 h post-meal (-7.5 mm Hg) and persisted for 3.5 h (-5 mm Hg) (101).

Green vegetables are also high in lutein, a carotenoid that possesses antioxidant and anti-inflammatory properties (102). Those highest in lutein include asparagus, broccoli, green beans, kale, parsley, spinach, and zucchini. In the CARDIA (Coronary Artery Risk Development in Young Adults) study, lutein was inversely related to incident hypertension, and other epidemiological studies have found that increased lutein consumption correlated with reduced atherosclerosis and risk of CVD (103,104).

Green leafy vegetables are associated with reduced incidence of T2DM. A large meta-analysis of 434,342 participants found that for each increment of 0.2 servings daily (approximately 1 oz), there was a 13% lower risk of developing T2DM (105). Potential mechanisms for this association include the high fiber and antioxidant content of these foods, which are associated with improved insulin sensitivity, and appreciable amounts of magnesium, which is independently and inversely correlated with T2DM (106).

Green vegetables exhibit other cardioprotective properties. For example, celery contains 3-n-butylphthalide, a vasodilatory compound that has been reported to reduce blood pressure in hypertensive subjects (107). Asparagus contains the antioxidant rutin, recently found to possess anticlotting properties (108). Green vegetables, such as broccoli, Brussels sprouts, collard greens, kale, and kohlrabi originate from the species *Brassica oleracea*, and contain sulforaphane and anthocyanins, bioactive compounds that protect against myocardial oxidative damage, and reduce infarct size and cell death in animal models. Small studies of relatively short duration (3 months) have demonstrated reduction of LDL-C levels and LDL oxidation (109). In the NHS and the HPFS, in which nearly 110,000 women and men were followed for 14 to 16 years, 3 servings a day of green leafy vegetable intake combined with a low-carbohydrate diet elicited a 24% reduced risk of CVD (110).

In patients receiving warfarin therapy, green leafy vegetables should not be discouraged because of concerns that its high vitamin K content will reduce anticoagulant effectiveness. Rather, once the therapeutic window of warfarin is established on a diet that includes green leafy vegetables, it is important to emphasize that the amount consumed should remain relatively constant on a daily basis.

Green leafy vegetables: the bottom line. A dietary pattern that is rich in a variety of green leafy vegetables has significant beneficial effects on ASCVD risk factors and is associated with reduced ASCVD risk. Careful guidance should be provided to patients on warfarin to establish a stable, consistent intake to avoid variations in the efficacy of anticoagulation.

JUICING: A PATH TO HEART HEALTH? Juicing of fruits and vegetables, often in combination with other foods and nutritional supplements, has become very popular, with no end of technologies to prepare the elixirs of health. However, the process of juicing concentrates calories, which makes it much easier to ingest excessive energy. There is evidence that phytochemical nutrients, such as lycopene, exhibit greater bioavailability in a liquid form versus the whole food (111). There are few studies evaluating the clinical benefits of vegetable juicing versus raw or cooked forms. One study that tested carotenoid-rich or control vegetable soups over 4 weeks reported increases in plasma carotenoids, although a control group was not included (112). Similarly, recent studies using a combination of fruit and vegetable pureed drinks found improved antioxidant capacity and vasoreactivity, although there was no comparator (i.e., consumption of whole fruits and vegetables) (112,113).

Juicing: the bottom line. Until comparative data become available, whole food consumption is preferred, with juicing primarily reserved for situations when daily intake of vegetables and fruits is inadequate. Guidance should be provided to maintain optimal overall caloric intake and to avoid the addition of sugars (e.g., honey) to minimize caloric overconsumption.

THE PLANT-BASED DIET. Whole food plant-based dietary patterns are becoming increasingly popular because of a variety of reported health benefits. A vegan dietary pattern is devoid of all animal products, whereas a vegetarian diet is typically a nonmeat diet, but can include milk products and eggs. All plants contain protein, but in variable amounts. Pound for pound (dry weight), vegetable protein-rich foods, such as legumes, contain as much or more protein than most animal foods, without the

sodium or fat. One cup of cooked lentils contains 18 g of protein (and no fat or sodium). For comparison, an average 6-oz steak may have up to 40 g protein, but also has 12 g of SFAs, which is nearly two-thirds of the recommended daily allotment (114). It is not necessary to intentionally combine or “complement” plant foods to obtain adequate protein (115). Although the quantities of essential amino acids vary from 1 food to another, nearly all plant-derived foods contain most of the essential amino acids. Including foods from a variety of plant sources can provide adequate quantities with careful diet planning.

Epidemiological studies and RCTs indicate that plant-based diets are associated with improvement in ASCVD risk factors and a decreased risk of ASCVD. Studies have been conducted both for the prevention and treatment of CVD with plant-based diets, often in conjunction with other heart-healthy lifestyle behaviors.

In the European Prospective Investigation into Cancer and Nutrition, 44,561 men and women were followed for 11.6 years. Of the participants, 15,151 (34%) were vegetarians (consuming no meat or fish) (116). Vegetarians had a lower mean BMI, lower non-HDL-C, lower systolic blood pressure, and a 32% lower risk of developing CHD. In the United States, vegetarian dietary patterns are associated with lower prevalence of T2DM and metabolic syndrome (117,118). Meta-analyses have also shown that, compared with omnivorous dietary patterns, vegetarian dietary patterns are associated with healthier body weight and blood pressure (119,120).

In a systematic review and meta-analysis of 8 studies with a Seventh Day Adventist population ($n = 183,321$), there was a reduced risk of CHD events (RR: 0.60; 95% CI: 0.43 to 0.80 vs. RR: 0.84; 95% CI: 0.74 to 0.96) and cerebral vascular disease events (RR: 0.71; 95% CI: 0.41 to 1.20 vs. RR: 1.05; 95% CI: 0.89 to 1.24) in vegetarians compared with non-vegetarians (121). Furthermore, populations consuming a predominantly plant-based diet are reported to rarely develop CVD. These include the Okinawans, the Papua Highlanders of New Guinea, the rural Chinese, central Africans, and the Tarahumara of northern Mexico (122-126).

Clinical trials have also demonstrated benefits of plant-based dietary patterns in patients with CHD. In 1983 and 1990, RCTs using a lifestyle medicine intervention of a whole foods, low-fat, vegetarian diet, moderate exercise, social support, and stress-management training documented significant reversal in CHD, as measured by improvements in ventricular function using radionuclide

ventriculography, a 400% increase in myocardial perfusion by cardiac positron emission tomography, regression in coronary atherosclerosis using quantitative coronary arteriography, and 2.5 times fewer cardiac events when compared with a randomized control group (127-130). There was a dose-response correlation between adherence to this lifestyle intervention and changes in percent diameter stenosis. Two demonstration projects showed significant improvements in all risk factors, a >90% reduction in angina within weeks, decreased need for medications, and a 77% reduction in the need for revascularization (131,132). Additionally, in 1995 and 2014, a whole food plant-based diet intervention was shown to result in prevention of coronary artery disease progression and angiographic disease reversal (133-135). On this basis, it appears that a whole food, plant-based diet may halt progression of coronary atherosclerosis and achieve evidence of angiographic disease regression.

















Most recently, a large prospective cohort study of U.S. health care professionals described the association between animal versus plant protein intake and mortality outcomes (136). This study showed increased all-cause and CV mortality with high animal protein intake (including processed red meat, unprocessed red meat, and eggs). High plant protein intake was inversely associated with mortality rates. These findings are consistent with recommendations to increase plant protein intake and substitute plant protein for animal protein.

Plant-based diets and ASCVD: the bottom line. Evidence indicates that a diet that is predominantly plant based is associated with improved ASCVD risk factors, reduced CHD progression, and beneficial effects on ASCVD. A whole food, plant-based dietary pattern plays an important role in ASCVD risk reduction.

GLUTEN. For the 1% to 2% of the population with celiac disease (CD), a gluten-free diet reduces morbidity and mortality (137). There are 3 gluten-related disorders (GRDs): CD; wheat allergy; and nonceliac gluten sensitivity (NCGS) (138). NCGS is the source of most of the gluten controversy. Estimates suggest 6% or more of the population has NCGS (139). Although individuals with GRDs must avoid gluten, many others are following a gluten-free diet for perceived weight loss or health benefits. Although patients with CD typically present with malabsorption and weight loss, there is no evidence that avoidance of gluten by healthy individuals will result in weight loss or that gluten promotes weight gain (140-142). Some studies of patients with CD have

CENTRAL ILLUSTRATION Evidence for Cardiovascular Health Impact of Foods Reviewed

Summary of heart-harmful and heart-healthy foods/diets

 Evidence of harm; limit or avoid	 Inconclusive evidence; for harm or benefit	 Evidence of benefit; recommended
 Coconut oil and palm oil are high in saturated fatty acids and raise cholesterol	 Virgin coconut oil	 Extra-virgin olive oil reduces some CVD outcomes when consumed in moderate quantities
 Eggs have a serum cholesterol-raising effect	 High-dose antioxidant supplements	 Blueberries and strawberries (>3 servings/week) induce protective antioxidants
 Juicing of fruits/vegetables with pulp removal increases caloric concentration*	 Juicing of fruits/vegetables without pulp removal*	 30 g serving of nuts/day. Portion control is necessary to avoid weight gain.†
 Southern diets (added fats and oils, fried foods, eggs, organ and processed meats, sugar-sweetened drinks)	 Gluten-containing foods (for people without gluten-related disease)	 Green leafy vegetables have significant cardio-protective properties when consumed daily
		 Plant-based proteins are significantly more heart-healthy compared to animal proteins

Freeman, A.M. et al. J Am Coll Cardiol. 2017;69(9):1172-87.

This figure summarizes the foods discussed in this paper that should be consumed often, and others that should be avoided from a cardiovascular health perspective. *It is important to note that juicing becomes less of a benefit if calorie intake increases because of caloric concentration with pulp removal. †Moderate quantities are required to prevent caloric excess.

shown that subjects actually gain weight on a gluten-free diet (140,143,144). If a gluten-free diet is accomplished by controlling calories, then weight can be controlled and weight loss can be achieved (145). Although avoiding gluten is essential for patients with GRDs, it is critically important that patients consume a nutritionally adequate diet that meets energy needs. There is limited information about the effects of a gluten-free diet on CV risk factors in patients with CD, but there is no evidence for CV outcomes benefit of this dietary pattern (146).

Gluten: the bottom line. For patients with GRDs, a gluten-free diet that is rich in fruits and vegetables, legumes and dried beans, lean protein sources, nuts and seeds, low-fat dairy or nondairy alternatives rich in calcium and vitamin D, and healthy fats, including omega-3 fatty acids, plays an important role in management of symptoms. However, in patients without GRDs, many of the claims for health benefits are unsubstantiated.

A LOOK TO THE FUTURE

In summary, the future health of the global population largely depends on a shift to healthier dietary patterns (Central Illustration). However, in the search for the perfect dietary pattern and foods that provide miraculous benefits, consumers are vulnerable to unsubstantiated health benefit claims. As clinicians, it is important to stay abreast of the current scientific evidence to provide meaningful and effective nutrition guidance to patients for ASCVD risk reduction. In this brief review, just a few of the current trends in nutrition have been highlighted to serve as a starting point for the patient-clinician discussion. Available evidence supports CV benefits of nuts, olive oil and other liquid vegetable oils, plant-based diets and plant-based proteins, green leafy vegetables, and antioxidant-rich foods (Central Illustration). Although juicing may be of benefit for individuals who would otherwise not consume adequate amounts of fresh

fruits and vegetables, caution must be exercised to avoid excessive calorie intake. There is currently no evidence to supplement regular intake of antioxidant dietary supplements. Gluten is an issue for those with GRDs, and it is important to be mindful of this in routine clinical practice; however, there is no evidence for CV or weight loss benefits, apart from the potential caloric restriction associated with a gluten-free diet.

ACKNOWLEDGMENTS Barcelona and Ciber Fisiopatología de la Obesidad y Nutrición is an initiative of the Instituto de Salud Carlos III, Spain.

ADDRESS FOR CORRESPONDENCE: Dr. Andrew M. Freeman, Division of Cardiology, Department of Medicine, National Jewish Health, 1400 Jackson Street, J317, Denver, Colorado 80206. E-mail: andrew@docandrew.com.

REFERENCES

- Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2960-84.
- U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2010. 7th edition. Washington, DC: U.S. Government Printing Office, December 2010.
- U.S. Department of Agriculture and U.S. Department of Health and Human Services. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. Part A. Executive Summary. Available at: <http://www.health.gov/dietaryguidelines/2015-scientific-report/02-executive-summary.asp>. Accessed January 5, 2017.
- Gidding SS, Lichtenstein AH, Faith MS, et al. Implementing American Heart Association pediatric and adult nutrition guidelines: a scientific statement from the American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular Disease in the Young, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, and Council for High Blood Pressure Research. *Circulation* 2009;119:1161-75.
- Expert Panel on Integrated Guidelines for CV Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for CV health and risk reduction in children and adolescents: summary report. *Pediatrics* 2011;128 Suppl 5:S213-56.
- Maki KC, Slavlin JL, Rains TM, et al. Limitations of observational evidence: implications for evidence-based dietary recommendations. *Adv Nutr* 2014;5:7-15.
- Willett WC. Nutrition and chronic disease. *Public Health Rev* 1998;26:9-10.
- Byers T. The role of epidemiology in developing nutritional recommendations: past, present, and future. *Am J Clin Nutr* 1999;69:1304S-8S.
- Davies HT, Crombie IK. Bias in case-control studies. *Hosp Med* 2000;61:279-81.
- Kearns CE, Schmidt LA, Glantz SA. Sugar industry and coronary heart disease research: a historical analysis of internal industry documents. *JAMA Intern Med* 2016;176:1680-5.
- U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015-2020 Dietary Guidelines for Americans. 8th edition. December 2015. Available at: <http://health.gov/dietaryguidelines/2015/guidelines>. Accessed January 5, 2017.
- Shikany JM, Safford MM, Newby PK, et al. Southern dietary pattern is associated with hazard of acute coronary heart disease in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Circulation* 2015;132:804-14.
- Wang DD, Li Y, Chiuve SE, Stampfer MJ, et al. Association of specific dietary fats with total and cause-specific mortality. *JAMA Intern Med* 2016;176:1134-45.
- Dehghan M, Mente A, Teo KK, et al. Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET)/Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease (TRANSCEND) Trial Investigators. Relationship between healthy diet and risk of cardiovascular disease among patients on drug therapies for secondary prevention: a prospective cohort study of 31 546 high-risk individuals from 40 countries. *Circulation* 2012;126:2705-12.
- Li S, Chiuve SE, Flint A, et al. Better diet quality and decreased mortality among myocardial infarction survivors. *JAMA Intern Med* 2013;173:1808-19.
- Stewart RA, Wallentin L, Benatar J, et al. STABILITY Investigators. Dietary patterns and the risk of major adverse cardiovascular events in a global study of high-risk patients with stable coronary heart disease. *Eur Heart J* 2016;37:1993-2001.
- National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation* 2002;106:3143-421.
- Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington, DC: National Academies Press, 2002/2005.
- U.S. Department of Agriculture, U.S. Department of Health and Human Services. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. Washington, DC: U.S. Department of Health and Human Services, 2015.
- Hopkins PN. Effects of dietary cholesterol on serum cholesterol: a meta-analysis and review. *Am J Clin Nutr* 1992;55:1060-70.
- Weggemans RM, Zock PL, Katan M. Dietary cholesterol from eggs increase the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis. *Am J Clin Nutr* 2001;73:885-91.
- Ros E. Intestinal absorption of triglyceride and cholesterol. Dietary and pharmacological inhibition to reduce cardiovascular risk. *Atherosclerosis* 2000;151:357-79.
- Berger S, Raman G, Vishwanathan R, et al. Dietary cholesterol and cardiovascular disease: A systematic review and meta-analysis. *Am J Clin Nutr* 2015;102:276-94.
- United States Department of Agriculture Agricultural Research Service. National Nutrient Database for Standard Reference Release 28. Basic Report: 15271, Crustaceans, shrimp, cooked (not previously frozen). Available at: <https://ndb.nal.usda.gov/ndb/foods/show/4740?fgcd=&man=&facet=&count=&max=35&sort=&qlookup=shrimp&offset=&format=Abridged&new=&measureby>. Accessed January 5, 2017.
- DeLany JP, Windhauser MM, Champagne CM, et al. Differential oxidation of individual dietary fatty acids in humans. *Am J Clin Nutr* 2000;72:905-11.
- Feranil AB, Duazo PL, Kuzawa CW, et al. Coconut oil is associated with a beneficial lipid profile in pre-menopausal women in the Philippines. *Asia Pac J Clin Nutr* 2011;20:190-5.
- Assunção ML, Ferreira HS, dos Santos AF, et al. Effects of dietary coconut oil on the biochemical and anthropometric profiles of women presenting abdominal obesity. *Lipids* 2009;44:593-601.
- Marina AM, CheMan YB, Amin I. Virgin coconut oil: emerging functional food oil. *Trends Sci Food Technol* 2009;20:481-7.
- Babu AS, Veluswamy SK, Arena R, et al. Virgin coconut oil and its potential cardioprotective effects. *Postgrad Med* 2014;126:76-83.
- Prior I, Davidson F, Salmond C, et al. Cholesterol, coconuts and diet on Polynesian atolls: a natural experiment: the Pukapula and Tokelau island studies. *Am J Clin Nutr* 1981;34:1552-61.
- Jacobson TA, Maki KC, Orringer CE, et al., NLA Expert Panel. National Lipid Association

- recommendations for patient-centered management of dyslipidemia: part 2. *J Clin Lipidol* 2015;9:51-122.e1.
32. Eyres L, Eyres MF, Chisholm A, et al. Coconut oil consumption and cardiovascular risk factors in humans. *Nutr Rev* 2016;74:267-80.
33. Sun Y, Neelakantan N, Wu Y, et al. Palm oil consumption increases LDL cholesterol compared with vegetable oils low in saturated fat in a meta-analysis of clinical trials. *J Nutr* 2015;145:1549-58.
34. Chen BK, Seligman B, Farquhar JW, et al. Multi-Country analysis of palm oil consumption and cardiovascular disease mortality for countries at different stages of economic development: 1980-1997. *Global Health* 2011;7:45.
35. Kabagambe EK, Baylin A, Ascherio A, et al. The type of oil used for cooking is associated with the risk of nonfatal acute myocardial infarction in Costa Rica. *J Nutr* 2005;135:2674-9.
36. Lin L, Allemekinders H, Dansby A, et al. Evidence of health benefits of canola oil. *Nutr Rev* 2013;71:370-85.
37. Maki KC, Lawless AL, Kelley KM, et al. Corn oil improves the plasma lipoprotein lipid profile compared with extra-virgin olive oil consumption in men and women with elevated cholesterol: results from a randomized controlled feeding trial. *J Clin Lipidol* 2015;9:49-57.
38. Mensink RP, Zock PL, Kester ADM, et al. Effects of dietary fatty acids and carbohydrates on the ratio of total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* 2003;77:1146-55.
39. Estruch R, Martínez-González MA, Corella D, et al., PREDIMED Study Investigators. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med* 2006;145:1-11.
40. Covas MI, Nyssönen K, Poulsen HE, et al., EUROLIVE Study Group. The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial. *Ann Intern Med* 2006;145:333-41.
41. Hernáez Á, Fernández-Castillejo S, Farràs M, et al. Olive oil polyphenols enhance high-density lipoprotein function in humans: a randomized controlled trial. *Arterioscler Thromb Vasc Biol* 2014;34:2115-9.
42. Schwingshackl L, Christoph M, Hoffmann G. Effects of olive oil on markers of inflammation and endothelial function: a systematic review and meta-analysis. *Nutrients* 2015;7:7651-75.
43. Schwingshackl L, Hoffmann G. Mono-unsaturated fatty acids, olive oil and health status: a systematic review and meta-analysis of cohort studies. *Lipids Health Dis* 2014;13:154.
44. Guasch-Ferré M, Hruby A, Salas-Salvadó J, et al. Olive oil consumption and risk of type 2 diabetes in US women. *Am J Clin Nutr* 2015;102:479-86.
45. Estruch R, Ros E, Salas-Salvadó J, et al., PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet [Published correction appears in *N Engl J Med*. 2014;370:886]. *N Engl J Med* 2013;368:1279-90.
46. Bester D, Esterhuysen AJ, Truter EJ, et al. Cardiovascular effects of edible oils: a comparison between four popular edible oils. *Nutr Res Rev* 2010;23:334-48.
47. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2011;123:2292-333.
48. Produce for Better Health Foundation. State of the Plate, 2015 Study on America's Consumption of Fruit and Vegetables, Produce for Better Health Foundation, 2015. Available at: http://www.pbhfoundation.org/pdfs/about/res/pbh_res/State_of_the_Plate_2015_WEB_Bookmarked.pdf. Accessed January 5, 2017.
49. Wu X, Beecher GR, Holden JM, et al. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. *J Agric Food Chem* 2006;54:4069-75.
50. Wedick NM, Pan A, Cassidy A, et al. Dietary flavonoid intakes and risk of type 2 diabetes in US men and women. *Am J Clin Nutr* 2012;95:925-33.
51. Cassidy A, Mukamal KJ, Liu L, et al. High anthocyanin intake is associated with a reduced risk of myocardial infarction in young and middle-aged women. *Circulation* 2013;127:188-96.
52. Johnson SA, Figueroa A, Navaei N, et al. Daily blueberry consumption improves blood pressure and arterial stiffness in postmenopausal women with pre- and stage 1-hypertension: a randomized, double-blind, placebo-controlled clinical trial. *J Acad Nutr Diet* 2015;115:369-77.
53. Muraki I, Imamura F, Manson JE, et al. Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. *BMJ* 2013;347:f5001.
54. Boeing H, Bechthold A, Bub A, et al. Critical review: vegetables and fruit in the prevention of chronic diseases. *Eur J Nutr* 2012;51:637-63.
55. Slavin J, Lloyd B. Health benefits of fruits and vegetables. *Adv Nutr* 2012;3:506-16.
56. Wang S, Melnyk JP, Tsao R, et al. How natural dietary antioxidants in fruits, vegetables and legumes promote vascular health. *Food Res Int* 2011;44:14-22.
57. Papas AM. Diet and antioxidant status. *Food Chem Toxicol* 1999;37:999-1007.
58. Harman D. Aging: A theory based on free radical and radiation chemistry. *J Gerontol* 1956;11:298-300.
59. Sies H. Oxidative stress: oxidants and antioxidants. *Exp Physiol* 1997;82:291-5.
60. Heitzer T, Schlinzig T, Krohn K, et al. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease [Published correction appears in *Circulation* 2003;108:500]. *Circulation* 2001;104:2673-8.
61. Reuter S, Gupta SC, Chaturvedi MM, et al. Oxidative stress, inflammation, and cancer: how are they linked? *Free Radic Biol Med* 2010;49:1603-16.
62. Wruck CJ, Fragoulis A, Gurzynski A, et al. Role of oxidative stress in rheumatoid arthritis: insights from the Nrf2-knockout mice. *Ann Rheum Dis* 2011;70:844-50.
63. Moylan JS, Reid MB. Oxidative stress, chronic disease, and muscle wasting. *Muscle Nerve* 2007;35:411-29.
64. Perry G, Cash AD, Smith M. Alzheimer disease and oxidative stress. *J Biomed Biotechnol* 2002;2:120-3.
65. Jenner P. Oxidative stress in Parkinson's disease. *Ann Neurol* 2003;53 Suppl 3:S26-36; discussion S36-8.
66. Stampfer MJ, Hennekens CH, Manson JE. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med* 1994;328:1444-9.
67. Losonczy KG, Harris TB, Havlik RJ. Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the Established Populations for Epidemiologic Studies of the Elderly. *Am J Clin Nutr* 1996;64:190-6.
68. Enstrom JE, Kanim LE, Klein MA. Vitamin C intake and mortality among a sample of the United States population. *Epidemiology* 1992;3:194-202.
69. Chun OK, Floegel A, Chung SJ, et al. Estimation of antioxidant intakes from diet and supplements in U.S. adults [Published correction appears in *J Nutr* 2010;140:1062]. *J Nutr* 2010;140:317-24.
70. Bailey RL, Gahche JJ, Lentino CV, et al. Dietary supplement use in the United States, 2003-2006. *J Nutr* 2011;141:261-6.
71. GISSI-Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;354:447-55.
72. Vivekananthan DP, Penn MS, Sapp SK, et al. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet* 2003;361:2017-23.
73. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996;334:1145-9.
74. Bjelakovic G, Nikolova D, Simonetti RG, et al. Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. *Lancet* 2004;364:1219-28.
75. Lawson KA, Wright ME, Subar A, et al. Multi-vitamin use and risk of prostate cancer in the National Institutes of Health-AARP Diet and Health Study. *J Natl Cancer Inst* 2007;99:754-64.
76. Mattson MP. Hormesis defined. *Ageing Res Rev* 2008;7:1-7.
77. Yang W, Hekimi S. A mitochondrial superoxide signal triggers increased longevity in *Caenorhabditis elegans*. *PLoS Biol* 2010;8:e1000556.
78. Bjelakovic G, Glud C. Surviving antioxidant supplements. *J Natl Cancer Inst* 2007;99:742-3.
79. Moyer MW. The myth of antioxidants. *Sci Am* 2013;308:62-7.

- 80.** Pérez V, Bokov A, Remmen H, et al. Is the oxidative stress theory of aging dead? *Biochim Biophys Acta* 2009;1790:1005-14.
- 81.** Mattson MP. What doesn't kill you.... *Sci Am* 2015;313:40-5.
- 82.** Hasnain BI, Mooradian AD. Recent trials of antioxidant therapy: what should we be telling our patients? *Cleve Clin J Med* 2004;71:327-34.
- 83.** Ros E. Health benefits of nut consumption. *Nutrients* 2010;2:652-82.
- 84.** Afshin A, Micha R, Khatibzadeh S, et al. Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis. *Am J Clin Nutr* 2014;100:278-88.
- 85.** Vigiouliou E, Kendall CW, Blanco Mejia S, et al. Effect of tree nuts on glycemic control in diabetes: a systematic review and meta-analysis of randomized controlled dietary trials. *PLoS One* 2014; 9:e103376.
- 86.** Zhou D, Yu H, He F, et al. Nut consumption in relation to cardiovascular disease risk and type 2 diabetes: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr* 2014;100: 270-7.
- 87.** Sabaté J, Oda K, Ros E. Nut consumption and blood lipids: a pooled analysis of 25 intervention trials. *Arch Intern Med* 2010;170:821-7.
- 88.** Salas-Salvadó J, Fernández-Ballart J, Ros E, et al., PREDIMED Study Investigators. Effect of the Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch Intern Med* 2008;168:2449-58.
- 89.** Babio N, Toledo E, Estruch R, et al., PREDIMED Study Investigators. Mediterranean diets and metabolic syndrome status in the PREDIMED randomized trial. *CMAJ* 2014;186:E649-57.
- 90.** Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Published correction appears in *J Am Coll Cardiol* 2014;63: 3027-8]. *J Am Coll Cardiol* 2014;63:2960-84.
- 91.** Luo C, Zhang Y, Ding Y, et al. Nut consumption and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis. *Am J Clin Nutr* 2014;100:256-69.
- 92.** Grosso G, Yang J, Marventano S, et al. Nut consumption on all-cause, cardiovascular, and cancer mortality risk: a systematic review and meta-analysis of epidemiologic studies. *Am J Clin Nutr* 2015;101:783-93.
- 93.** Meschia JF, Bushnell C, Boden-Albala B, et al., American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Functional Genomics and Translational Biology, and Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:3754-832.
- 94.** Bes-Rastrollo M, Wedick NM, Martínez-González MA, et al. Prospective study of nut consumption, long-term weight change, and obesity risk in women. *Am J Clin Nutr* 2009;89: 1913-9.
- 95.** Ibarrola-Jurado N, Bulló M, Guasch-Ferré M, et al., PREDIMED Study Investigators. Cross-sectional assessment of nut consumption and obesity, metabolic syndrome and other cardiometabolic risk factors: the PREDIMED study. *PLoS One* 2013;8:e57367.
- 96.** Flores-Mateo G, Rojas-Rueda D, Basora J, et al. Nut intake and adiposity: meta-analysis of clinical trials. *Am J Clin Nutr* 2013;97:1346-55.
- 97.** Jackson CL, Hu FB. Long-term associations of nut consumption with body weight and obesity. *Am J Clin Nutr* 2014;100 Suppl 1: 408S-11S.
- 98.** Estruch R, Martínez-González MA, Corella D, et al., PREDIMED Study Investigators. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. *Lancet Diabetes Endocrinol* 2016; 4:666-76.
- 99.** Rajaram S, Sabaté J. Nuts, body weight and insulin resistance. *Br J Nutr* 2006;96 Suppl 2: S79-86.
- 100.** Bondonno CP, Liu AH, Croft KD, et al. Short-term effects of a high nitrate diet on nitrate metabolism in healthy individuals. *Nutrients* 2015; 7:1906-15.
- 101.** Liu AH, Bondonno CP, Croft KD, et al. Effects of a nitrate-rich meal on arterial stiffness and blood pressure in healthy volunteers. *Nitric Oxide* 2013;35:123-30.
- 102.** Woodside JV, McGrath AJ, Lyner N, et al. Carotenoids and health in older people. *Maturitas* 2015;80:63-8.
- 103.** Hozawa A, Jacobs DR Jr., Steffes MW, et al. Circulating carotenoid concentrations and incident hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *J Hypertens* 2009;27:237-42.
- 104.** Gammone MA, Riccioni G, D'Orazio N. Carotenoids: potential allies of cardiovascular health? *Food Nutr Res* 2015;59:26762.
- 105.** Li M, Fan Y, Zhang X, et al. Fruit and vegetable intake and risk of type 2 diabetes mellitus: meta-analysis of prospective cohort studies. *BMJ Open* 2014;4:e005497.
- 106.** Larsson SC, Wolk A. Magnesium intake and risk of type 2 diabetes: a meta-analysis. *J Intern Med* 2007;262:208-14.
- 107.** Houston MC. Nutraceuticals, vitamins, antioxidants, and minerals in the prevention and treatment of hypertension. *Prog Cardiovasc Dis* 2005;47:396-449.
- 108.** Jassu R, Passam FH, Kennedy DR, et al. Protein disulfide isomerase inhibitors constitute a new class of antithrombotic agents. *J Clin Invest* 2012;122:2104-13.
- 109.** Pagliaro B, Santolamazza C, Simonelli F, et al. Phytochemical compounds and protection from cardiovascular diseases: a state of the art. *Biomed Res Int* 2015;2015:918069.
- 110.** Joshupura KJ, Hung HC, Li TY, et al. Intakes of fruits, vegetables and carbohydrate and the risk of CVD. *Public Health Nutr* 2009;12:115-21.
- 111.** Böhm V, Bitsch R. Intestinal absorption of lycopene from different matrices and interactions to other carotenoids, the lipid status, and the antioxidant capacity of human plasma. *Eur J Nutr* 1999;38:118-25.
- 112.** Paterson E, Gordon MH, Niwat C, et al. Supplementation with fruit and vegetable soups and beverages increases plasma carotenoid concentrations but does not alter markers of oxidative stress or cardiovascular risk factors. *J Nutr* 2006; 136:2849-55.
- 113.** George TW, Waroonphan S, Niwat C, et al. Effects of acute consumption of a fruit and vegetable purée-based drink on vasodilation and oxidative status. *Br J Nutr* 2013;109:1442-52.
- 114.** United States Department of Agriculture, Agriculture Research Service. USDA Nutrient Database for Standard Reference, Release 14. 2001. Available at: [http://www.ars.usda.gov/ Services/docs.htm?docid=21215](http://www.ars.usda.gov/Services/docs.htm?docid=21215). Accessed January 5, 2017.
- 115.** Position of the American Dietetic Association: vegetarian diets. *J Am Diet Assoc* 2009;109: 1266-82.
- 116.** Crowe FL, Appleby PN, Travis RC, et al. Risk of hospitalization or death from ischemic heart disease among British vegetarians and non-vegetarians: results from the EPIC-Oxford Cohort Study. *Am J Clin Nutr* 2013;97:597-603.
- 117.** Tonstad S, Butler T, Yan R, Fraser GE. Type of vegetarian diet, body weight, and prevalence of type 2 diabetes. *Diabetes Care* 2009;32:791-6.
- 118.** Rizzo NS, Sabaté J, Jaceldo-Siegl K, et al. Vegetarian dietary patterns are associated with a lower risk of metabolic syndrome: the Adventist Health Study 2. *Diabetes Care* 2011;34:11225-7.
- 119.** Yokoyama Y, Nishimura K, Barnard ND, et al. Vegetarian diets and blood pressure: a meta-analysis. *JAMA Intern Med* 2014;174:577-87.
- 120.** Barnard ND, Levin SM, Yokoyama Y. A systematic review and meta-analysis of changes in body weight in clinical trials of vegetarian diets. *J Acad Nutr Diet* 2015;115:954-69.
- 121.** Kwok CS, Umar S, Myint PK, et al. Vegetarian diet, Seventh Day Adventist and risk of cardiovascular mortality: a systematic review and meta-analysis. *Int J Cardiol* 2014;176:680-6.
- 122.** Willcox B, Willcox D, Todoriki H, et al. Caloric restriction, the traditional Okinawan diet, and healthy aging. *Ann NY Acad Sci* 2001;1114:434-55.
- 123.** Sinnett PF, Whyte HM. Epidemiological studies in a total highland population, Tukisenta, New Guinea. Cardiovascular disease and relevant clinical, electrocardiographic, radiological and biochemical findings. *J Chron Dis* 1973;26:265-90.
- 124.** Campbell TC, Parpia B, Chen J. Diet, lifestyle, and the etiology of coronary artery disease: the Cornell China study. *Am J Cardiol* 1998;82: 18T-21T.
- 125.** Miller K, Rubenstein A, Astrand PO. Lipid values in Kalahari bushmen. *Arch Intern Med* 1968;121:414-7.

- 126.** Connor WE, Cerqueira MT, Connor RW, et al. The plasma lipids, lipoproteins, and diet of the Tarahumara Indians of Mexico. *Am J Clin Nutr* 1978;31:1131-42.
- 127.** Ornish DM, Scherwitz LW, Doody RS, et al. Effects of stress management training and dietary changes in treating ischemic heart disease. *JAMA* 1983;249:54-9.
- 128.** Gould KL, Ornish D, Scherwitz L, et al. Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. *JAMA* 1995;274:894-901.
- 129.** Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary artery disease? The Lifestyle Heart Trial. *Lancet* 1990;336:129-33.
- 130.** Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary artery disease [Published correction appears in *JAMA* 1999;281:1380]. *JAMA* 1998;280:2001-7.
- 131.** Ornish D. Avoiding revascularization with lifestyle changes: The Multi Center Lifestyle Demonstration Project. *Am J Cardiol* 1999;82:72T-6T.
- 132.** Silberman A, Banthia R, Estay IS, et al. The effectiveness and efficacy of an intensive cardiac rehabilitation program in 24 sites. *Am J Health Promot* 2010;24:260-6.
- 133.** Esselstyn CB Jr., Ellis SG, Medendorp SV, et al. A strategy to arrest and reverse coronary artery disease; a 5-year longitudinal study of a single physician's practice. *J Fam Prac* 1995;41:560-8.
- 134.** Esselstyn CB Jr. Updating a 12-year experience with arrest and reversal therapy for coronary heart disease (an overdue requiem for palliative cardiology). *Am J Cardiol* 1999;84:339-41.
- 135.** Esselstyn CB Jr., Gendy G, Doyle J, et al. A way to reverse CAD? *J Fam Prac* 2014;63:356-64b.
- 136.** Song M, Fung TT, Hu FB, et al. Association of animal and plant protein intake with all-cause and cause-specific mortality. *JAMA Intern Med* 2016;176:1453-63.
- 137.** Lundin KE, Wijmenga C. Coeliac disease and autoimmune disease-genetic overlap and screening. *Nat Rev Gastroenterol Hepatol* 2015;12:507-15.
- 138.** Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. *Gut* 2013;62:43-52.
- 139.** Lebowitz B, Ludvigsson JF, Green PH. Celiac disease and non-celiac gluten sensitivity. *BMJ* 2015;351:h4347.
- 140.** Dickey W, Kearney N. Overweight in celiac disease: prevalence, clinical characteristics, and effect of a gluten-free diet. *Am J Gastroenterol* 2006;101:2356-9.
- 141.** El-Chammas K, Danner E. Gluten-free diet in nonceliac disease. *Nutr Clin Pract* 2011;26:294-9.
- 142.** Marcason W. Is there evidence to support the claim that a gluten-free diet should be used for weight loss? *J Am Diet Assoc* 2011;111:1786.
- 143.** Theethira TG, Dennis M. Celiac disease and the gluten-free diet: consequences and recommendations for improvement. *Dig Dis* 2015;33:175-82.
- 144.** Valletta E, Fornaro M, Cipolli M, et al. Celiac disease and obesity: need for nutritional follow-up after diagnosis. *Eur J Clin Nutr* 2010;64:1371-2.
- 145.** Ebbeling CB, Swain JF, Feldman HA, et al. Effects of dietary composition on energy expenditure during weight-loss maintenance. *JAMA* 2012;307:2627-34.
- 146.** Zanini B, Mazzoncini E, Lanzarotto F, et al. Impact of gluten-free diet on cardiovascular risk factors. A retrospective analysis in a large cohort of coeliac patients. *Dig Liver Dis* 2013;45:810-5.

KEY WORDS cardiovascular risk, fats, green leafy vegetables, healthy dietary patterns, nutrition